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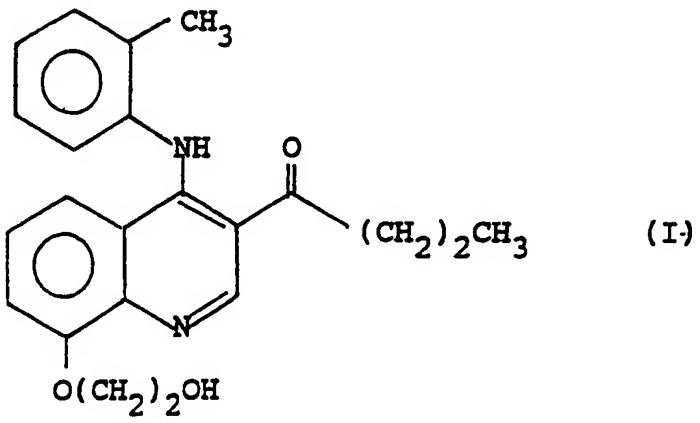
(54) Title: SALTS OF A 4-AMINO-3-ACYL QUINOLINE DERIVATIVE AND THEIR USE AS INHIBITORS OF GASTRIC ACID SECRETION



(I)

(57) Abstract

A compound of structure (I) in the form of a salt, a process for its preparation and pharmaceutical compositions comprising such a salt and its use in therapy.

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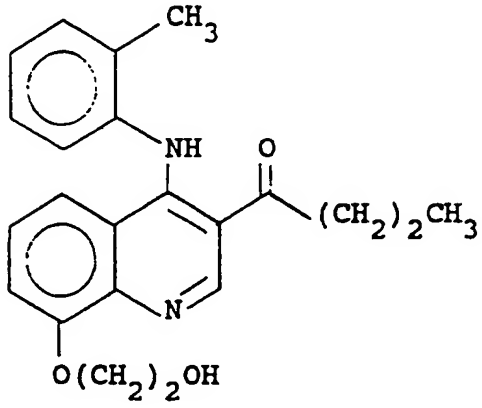
Salts of a 4-amino-3-acyl quinoline derivative and their use as inhibitors of gastric acid secretion.

The present invention relates to certain salts of a quinoline compound, pharmaceutical compositions containing them and their use in therapy as inhibitors of gastric acid secretion.

Quinoline compounds which have activity as gastric acid secretion inhibitors are known in the art, for example, EP-330485-A discloses a series of 4-amino-3-acylquinoline derivatives in which the quinoline is substituted in the 8-position by, for example, hydroxyalkyl and hydroxyalkoxy groups.

The compounds of EP 330485-A have been found to have poor dissolution rates in water and, as a consequence, could potentially exhibit poor bioavailability in vivo and hence low and poorly reproducible levels of therapeutic activity. It has now been found that the problem of poor dissolution can be overcome by producing the compounds in the form of a particular class of salts. Furthermore, in selecting compounds for use in therapy it is important to take a number or criteria into account, for example, in addition to physical qualities such as good dissolution (and hence good bioavailability), the desired level of intrinsic potency and duration of action of the chosen compounds has to be at the desired level. It has been found that a particular compound of EP-330485-A when produced in the form of a salt as described herein, in addition to having the desired physical qualities such as a high dissolution rate, also has the desired levels of potency and duration of action and, as such, form the subject matter of the present invention.

The present invention therefore provides in a first aspect a compound of structure (I):



(I)

in the form of a salt characterised in that the salt is that formed by reaction of said compound of structure (I) with a strong acid.

As used herein, the term strong acid shall be taken to mean an acid with a pka of less than about 4.0. The nature of such acids will be apparent to those skilled in the art and include, for example, mineral acids such as hydrochloric acid, and sulphonic acids such as alkyl sulphonic acids, in particular methane sulphonic acid.

Particularly preferred salts of the present invention are those formed by reaction with hydrochloric acid or methane sulphonic acid, that is to say, 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline hydrochloride, and 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline mesylate.

The salts of the present invention, in particular the hydrochloride and mesylate salts referred to above, have been found to exhibit exceptionally fast intrinsic dissolution rates when compared to the free base compound of structure (I) disclosed in EP-330485-A. Thus,

whereas the free base has a poor dissolution rate and, as such, may be expected in vivo to exhibit poorly reproducible bioavailability (and so be less effective therapeutically), the salts of the present invention are expected to exhibit a much more consistent bioavailability (since their dissolution rates are far more favourable) and to prove more effective per given dose and more reliably effective per given dose on administration to patients.

The salts described herein can be used in therapy in the treatment of gastrointestinal diseases in mammals, in particular humans. Such diseases include, for example, gastric and duodenal ulcers, aspiration pneumonitis and Zollinger-Ellison syndrome. Further, the salts can be used in the treatment of other disorders where an anti-secretory effect is desirable, for example in patients with a history of chronic and excessive alcohol consumption, and in patients with gastrooesophageal reflux disease (GERD).

In therapeutic use, the salts can be administered in a standard pharmaceutical composition comprising the salt and a pharmaceutically acceptable carrier. The present invention provides in a further aspect therefore a pharmaceutical composition comprising a salt as described herein in association with a pharmaceutically acceptable carrier.

Suitable pharmaceutical compositions are as described in EP-330485-A.

Suitable daily dosage regimens for an adult patient may be, for example, an oral dose of between 1 and 1000 mg, preferably between 1 and 500 mg, or an

intravenous, subcutaneous or intramuscular dose of between 0.1 and 100 mg, preferably between 0.1 and 25 mg of the salts described herein, the salt being administered in a unit dosage 1 to 4 times a day.

In addition, the salts can be co-administered with further active ingredients such as antacids (for example, magnesium carbonate or hydroxide and aluminium hydroxide), non-steroidal anti-inflammatory drugs, steroids or nitrite scavengers or other drugs used for treating gastric ulcers (for example, prostanoids or H_2-antagonists such as cimetidine).

EXAMPLE 1

3-Butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline can be prepared according to the procedures described in EP-330485-A.

Preparation of 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline hydrochloride

3-Butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline (10 g) was suspended in methanol (100 ml) at room temperature, conc. hydrochloric acid added slowly to give a clear solution, then the solvent evaporated. The residue was twice taken up in 2-propanol and re-evaporated, and was then recrystallised from 2-propanol/ether to obtain the desired salt (9.7 g), m.p. 214-215°C.

$C_{22}H_{24}N_2O_3.HCl.0.2H_2O$

Found C 65.50, H 6.21, N 6.88

Requires C 65.32, H 6.33, N 6.93.

EXAMPLE 2

Preparation of 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline mesylate

3-Butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline (60 g) was suspended in ethyl acetate (400 ml), warmed to 50°C, and methanesulphonic acid (16.3 g) added with vigorous stirring. The desired salt crystallised on cooling, and was filtered off and washed with ethyl acetate; yield 50.1 g, m.p. 83-85°C.

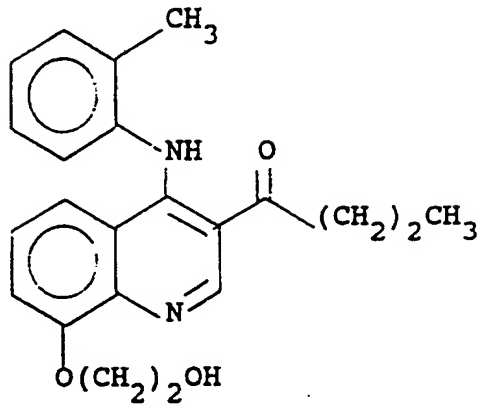
$C_{22}H_{24}N_2O_3.CH_4O_3S.H_2O$

Found C 57.78, H 6.28, N 5.84

Requires C 57.73, H 6.32, N 5.85.

Claims

1. A compound of structure (I):



(I)

in the form of a salt, characterised in that the salt is that formed by reaction of the compound of structure (I) with a strong acid.

2. A salt according to claim 1 which is 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline hydrochloride.

3. A salt according to claim 1 which is 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline mesylate.

4. A process for preparing a salt according to claim 1 which comprises reacting a compound of structure (I) as described in claim 1 with a strong acid.

5. A pharmaceutical composition comprising a salt according to claim 1 in association with a pharmaceutically acceptable carrier.

6. A pharmaceutical composition comprising 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline hydrochloride in association with a pharmaceutically acceptable carrier.

7. A salt according to claim 1 for use in therapy.

8. 3-Butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline hydrochloride for use in therapy.

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D215/44; A61K31/47

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 330 485 (SMITHKLINE BECKMAN INTERCREDIT B.V.) 30 August 1989 cited in the application see page 3, line 19 - line 23 see page 6, line 31 - line 34; claims 1,6-9; example 10 ---	1-8

° Special categories of cited documents :[10]

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03 APRIL 1992	12.05.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P. BOSMA

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9200200 SA 55460

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0330485	30-08-89	AU-B- 606508	07-02-91
		AU-A- 3181989	22-09-89
		WO-A- 8908104	08-09-89
		JP-T- 2503318	11-10-90